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Case Report on Dapagliflozin Induced Thrombocytopenia

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ABSTRACT
Drug-induced immune thrombocytopenia (DITP), is defined as an acute, often severe decrease in platelet count which is usually caused due to various drugs and involves multiple mechanisms. Here, we report a rare case of DITP caused by Dapagliflozin,an inhibitor of the sodium-glucose co-transporter-2 (SGLT2), used for the treatment of type 2 diabetes mellitus (T2DM). However, the underlying mechanismbehind the reduction in platelet level remains unclear. The patient was a 66 years old male who was admitted tothe general medicine department in a tertiary care hospital, Coimbatorewith complaints of difficulty in breathing for 1 hour. Upon admission, lab details revealed a reduced platelet count of 10,000/cumm^3. On evaluating the past medical history, he has been using oral Dapagliflozin 10 mg once daily in the afternoon for 4 years.Thrombocytopenia was proved to be Dapagliflozin-induced.Therefore,we recommended that platelet count should be regularly monitored in all patients receiving SGLT2 drugs including Dapagliflozin.

KEYWORDS: Drug-induced thrombocytopenia, Dapagliflozin, Type 2 diabetes mellitus.

I. INTRODUCTION

Thrombocytopenia is characterized by reduced platelet count <1,50,000/cumm3which is usually caused by various etiologic factors such asdrugs, chemicals, and some disease conditions that can also induce thrombocytopenia and platelet dysfunction.Although there are numerous hypoglycemic agents are available, therapeutic failure occurs owing to undetected ADRs.[1,2]DIT can be distinguished from idiopathic thrombocytopenic purpura (ITP), a bleeding disorder caused by thrombocytopenia not associated with a systemic disease.[3] Even though platelet dysfunction plays a major role in diabetic macrovascular complications, only a few studies have assessed the effect of oral hypoglycaemic agents (OHAs) on platelet function. [4] Despite the fact that the cause of thrombocytopenia is unclear, and the cliniciansare usually faced with various possible pathologies such as sepsis, disseminated intravascular coagulation, microangiopathic processes (hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura), and the use of certain drugs and components, including nutritional supplements or herbal remedies, can also cause thrombocytopenia by either inhibiting platelet production and/or enhancing their destruction from the peripheral blood mediated via drug-induced immune thrombocytopenia (DITP).[1]The diagnosis of drug-induced thrombocytopenia can be supported only by the resolution of thrombocytopenia after cessation of the suspected drug. In all epidemiological studies, the same class of drugs is mentioned as being the most frequently implicated: anti-diabetic drugs, NSAIDs, anticonvulsants, sulfonamides, diuretics, cinchona alkaloid derivatives, penicillamine.[8]Dapagliflozin, an inhibitor of the sodium-glucose co-transporter-2 (SGLT2), is used for the treatment of type 2 diabetes mellitus (T2DM).It will reduce the likelihood of hospitalization for heart failure and death in persons with type 2 diabetes, of which the mechanism has not been fully elucidated. The mechanistic effects of Dapagliflozin on platelet function profiles have not yet been ascertained. It remains unclear if this reduction in cardiovascular death is mediated by decreased platelet reactivity. Thrombin generation

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and platelet activation are increased in patients with T2DM.[5,6]The following case report will illustrate the Drug induced thrombocytopenia which was developed after the administration of Dapagliflozin, which has been already proven in a short review in the literature by C. Kohlmorgen et al.[5]

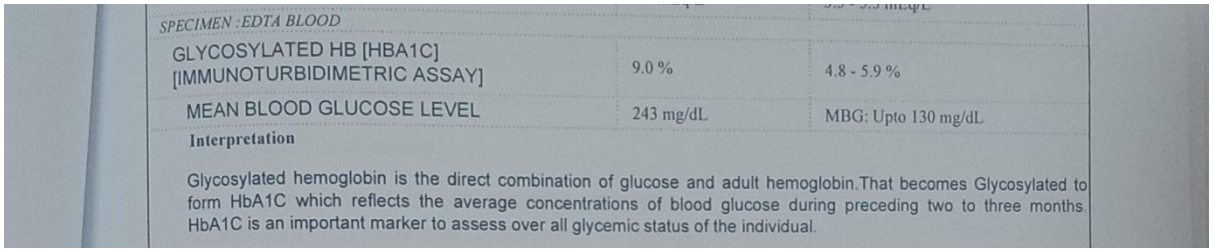
II. CASE REPORT

A 66 years old male was admitted in the general medicine department at a tertiary care hospital. He was admitted with complaints of dyspnoea for 2 hours and cough since morning. He wasa known case of Type 2 DM and was on Tab. OXRA 10mg for about 4 years, systemic hypertensionand was on Tab. PROLOMET XL 25 mg, Tab. LASILACTONE 20/0 mg for 1 yearsand CAD and was on Tab VYMADA 100 mg, Tab BRILLINTA 90 mg, Cap. ECOSPIRIN 75 mg and Tab. ROSUVIRON 20 mg.

Laboratory workup upon admission revealed isolated thrombocytopenia with a platelet level of 10,000/cumm^3, neutrophils was 82% on the day of admission. . His hemoglobin level was 11.8gm/dl and HbA1C was found to be 9%. However, no bleeding manifestations (gum bleeding, haematuria, melena).His peripheral smear showed normocytic normochromic anemia, with neutrophilic leucocytosis and thrombocytopenia with giant platelets present. Clinical suspicion of drug-induced thrombocytopenia prompted the discontinuation of Dapagliflozin, which resulted in a rapid increase in the number of platelets.

Upon literature review and evidence-based medicine, Tab. DAPAGLIFLOZIN was suspected to be the drug that induced thrombocytopenia. Therefore, it was stopped and the platelet count was repeatedly monitored for consecutive days. The patient showed clinical improvements during his hospitalization. On day 2, the platelet count was raised to 12,000/cumm^3, on day 3, the platelet count was 15,000/cumm^3, on day 4, the platelet count was 1, 00,000/cumm^3, and on day 5 it was increased to 1.5 lakhs/cumm^3.It is shown in Figure (1-5)

The patient was discharged after 5 days, having no symptoms and a platelet count of 1, 50,000/cumm^3. His discharge medication was Tab. GLIPTAGREATB 50/500 once in the morning and night, Tab. VOLIX 0.2 1 in the morning and once in the afternoon with food. Upon review, after once weekhis platelet count was found to be normal and his FBS was 197 mg/dl.



SPECIMEN :EDTA BLOOD

GLYCOSYLATED HB [HBA1C] [IMMUNOTURBIDIMETRIC ASSAY]	9.0 %	4.8 - 5.9 %
MEAN BLOOD GLUCOSE LEVEL	243 mg/dL	MBG: Upto 130 mg/dL

Interpretation

Glycosylated hemoglobin is the direct combination of glucose and adult hemoglobin.That becomes Glycosylated to form HbA1C which reflects the average concentrations of blood glucose during preceding two to three months. HbA1C is an important marker to assess over all glycemic status of the individual.

Figure 1: Laboratory data on admission

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Test Name	Result	Reference Value
SPECIMEN :EDTA BLOOD		
COMPLETE BLOOD COUNT [AUTOMATION]		
RBC COUNT [ELECTRICAL IMPEDANCE]	3.82 million/cumm	4.5 - 5.5 million/cumm
HB [PHOTOMETRY]	11.8 g/dL	13.0 - 17.0 g/dL
HCT [CALCULATED]	34.6 %	40 - 50 %
MCV [CALCULATED]	90.0 fL	83 - 101 fL
MCH [CALCULATED]	30.9 pg	27.0 - 32.0 pg
MCHC [CALCULATED]	34.2 g/dL	31.5 - 34.5 g/dL
PLATELET COUNT [ELECTRICAL IMPEDANCE]	Less than 10000 /cumm	150000 - 410000 /cumm
RDW CV [CALCULATED]	13.1 %	11.6 - 14.0 %
TOTAL COUNT [ELECTRICAL IMPEDANCE]	12600 /cumm	4000 - 10000 /cumm
DIFFERENTIAL COUNT		
Neutrophil [IMPEDANCE & LIGHT SCATTERING]	82.4 %	40 - 75 %
Lymphocyte [IMPEDANCE & LIGHT SCATTERING]	11.1 %	20 - 45 %
Monocyte [IMPEDANCE & LIGHT SCATTERING]	4.8 %	2 - 10 %
Eosinophil [IMPEDANCE & LIGHT SCATTERING]	1.1 %	1 - 6 %
Basophil [ELECTRICAL IMPEDANCE]	0.6 %	0 - 1 %
Comments :Giant platelets present. Repeated with fresh sample.		

Figure 2: Laboratory data on admission

Department :CLINICAL PATHOLOGY

Test Name	Result	Reference Value
PERIPHERAL SMEAR STUDY [SMEAR STUDY & MICROSCOPY]		

RBC: Reduced in number and show anisopoikilocytosis (+), and are normocytic normochromic. Polychromasia present,

elliptocytes (+), acanthocytes (+), tear drop cells present.

WBC: Total count is increased.

Neutrophils-80%, Lymphocytes-15%, Monocytes-04%, Eosinophils-01%.

Rise in neutrophils.

PLATELET: Reduced in number. Giant platelets present.

PARASITES: Not seen.

IMPRESSION: Normocytic normochromic anemia with neutrophilic leucocytosis and thrombocytopenia.

Figure 3: Laboratory data on admission

Test Name	Result	Reference Value
SPECIMEN :EDTA BLOOD		
PLATELET COUNT [ELECTRICAL IMPEDANCE]	12000 /cumm	150000 - 410000 /cumm
Comments :Giant platelets present.		

Figure 4: Laboratory data on day 2

Department :CLINICAL PATHOLOGY

Test Name	Result	Reference Value
SPECIMEN :EDTA BLOOD		
PLATELET COUNT [ELECTRICAL IMPEDANCE]	15000 /cumm	150000 - 410000 /cumm
Comments :Giant platelets present.		

Figure 5: Laboratory data on day 3

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III. DISCUSSION

Drug-induced immune thrombocytopenia is attributed to decrease in platelet production secondary to myelosuppression or accelerated platelet destruction secondary to an immune response. Drug-induced thrombocytopenia can present with asymptomatic thrombocytopenia, hemolytic-uremic syndrome (HUS), or thrombotic thrombocytopenicpurpura (TTP) in extreme cases.[7] Therefore, when the implicated drug is discontinued, platelet levels return to normal within a few days despite the continued presence of antibodies.Most cases of DITP are caused by drug-induced antibodies that bind to platelets only when the drug is present [9] Discontinuing the medication can boost up the platelet count with the short span of 4–8 days, although less commonly within weeks. The drugs used to treat diabetes mellitus are diverse and include several classes.[2,7]

Epidemiologic data suggest that DITP occurs in 10 cases per 1,000,000 population per year, although this is likely to be an underestimate.[1]As, Diabetes is highly predominant in our country, Dapagliflozin is considered to be the first-line treatment for diabetes in patients with cardiovascular complications (5 or 10 mg once daily).[6]

Dapagliflozin is in a class of medications called sodium-glucose co-transporter 2 (SGLT2) inhibitors, which reduces blood sugar by causing the kidneys to eliminate large amount of glucose in the urine. Dapagliflozin-induced thrombocytopenia was previously discussed by C. Kohlmorgen et al, which showed a decreased the percentage of CD62P-positive platelets in healthy humans indicating reduced platelet activation. Inline, Dapagliflozin decreased the percentage of activated CD62P-positive platelets also in atherosclerotic Ldlr-/-mice.[5]

Besides Dapagliflozin directly reduces CD62P expression on isolated platelets. Despite the significant effects on platelet activation, bleeding time was unaffected in Dapagliflozin-treated mice. There is not a report in literature about the use of Dapagliflozin and the development of thrombocytopenia but C. Kohlmorgen et al listed as Healthy human volunteers were treated with Dapagliflozin (10 mg/d) for 4 weeks. Platelet activation was measured before and after SGLT2 inhibition. Mice were analyzed after 8 and 25 weeks, respectively. After 4 weeks of treatment, Dapagliflozin decreased the percentage of CD62P-positive platelets in healthy humans indicating reduced platelet activation.[5]

We presented a rare case ofDapagliflozin-induced thrombocytopenia. In our case, bone marrow biopsy was normal and all the other causes of thrombocytopenia were excluded. Therefore, the suspected drug was found to beDapagliflozin and it was stopped at his admission. The thrombocyte count spontaneously increased in four days.We speculate that the development of thrombocytopenia, in this case, was due to the use of Dapagliflozin and this is the rare case of Dapagliflozin-induced thrombocytopenia in literature. In our case, thrombocytopenia developed more than one year after the initiation of treatment with Dapagliflozin. Dapagliflozin was stopped after admission tothe hospital and the platelets count was improved after stopping the drug.

IV. CONCLUSION

Dapagliflozin is a rare cause of severe thrombocytopenia that has been highlighted in our case. In this case, the patient experienced resolution of thrombocytopenia after the cessation of Dapagliflozin, although he had a delayed recovery time.Some oral antidiabetic drugs such as Dapagliflozin, Glibenclamide, and glimepiride are known to induce thrombocytopenia. So thrombocyte count must be checked regularly in patients receiving Dapagliflozin to rule out Drug-induced thrombocytopenia.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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